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Vascular Repair After Balloon Overstretch Injury in Porcine Model Effects of Intracoronary Radiation

Yves Cottin, MD, PHD,* Marc Kollum, MD,* Rosanna Chan, PHD,† Balram Bhargava, MD,* Yoram Vodovotz, PHD,* Ron Waksman, MD, FACC*

Washington, DC

OBJECTIVES The purpose of this study was to evaluate the effect of IR on thrombus formation and dissection repair following overstretch balloon injury in porcine coronary arteries.

BACKGROUND Exposure of blood to the injured arterial wall after percutaneous transluminal coronary angioplasty (PTCA) induces thrombus formation and inflammation in the dissection plane. Neointima formation is related to smooth muscle cell (SMC) proliferation and migration into the preformed thrombus. Intracoronary radiation (IR) with doses of 10 to 25 Gy using either beta or gamma emitters can prevent neointima accumulation by reducing SMC proliferation. However, there are some indications that IR may delay the process of dissection repair after PTCA. The purpose of this study was to evaluate the effect of IR on thrombus formation and dissection repair after overstretch balloon injury in porcine coronary arteries.

METHODS Forty porcine coronaries were injured by balloon overstretch followed by either 0 or 18 Gy of ^{90}Y prescribed to 1.2 mm from the balloon center. The animals were euthanized 14 days after treatment, and intimal area (IA) and IA corrected for medial fracture length (IA/FL) were quantified by digital image analysis. Dissections were quantified by tracing the length, thickness and area behind the dissection flap. The rate of dissections was calculated for each group. Thrombi were identified and designated as intraluminal thrombus or thrombus within dissection planes (mural thrombus), and area measurements were obtained.

RESULTS The irradiated group showed a significant reduction of IA/FL (0.55 ± 0.29 vs. 0.05 ± 0.09; $p < 0.001$). No difference was observed in the rate of dissection between control and irradiated arteries (77% vs. 88%, respectively). The control group showed a smaller dissection area (0.19 ± 0.28 mm^2 vs. 0.32 ± 0.29 mm^2; $p < 0.05$) with smaller mural thrombi (0.03 ± 0.01 mm^2 vs. 0.29 ± 0.30 mm^2; $p < 0.001$). A strong correlation between dissection area and neointima area was observed only in the control group ($R^2 = 0.474$; $p < 0.003$; $alpha_{0.05} = 0.862$). A positive correlation between mural thrombus and dissection area was observed only in the irradiated group ($R^2 = 0.889$; $p < 0.001$; $alpha_{0.05} = 1.00$).

CONCLUSIONS These results suggest that the dissection area may be a useful parameter by which to quantify the extent of injury and repair after IR and may indicate an incomplete healing process after IR at this time point. (J Am Coll Cardiol 2000;36:1389–95) © 2000 by the American College of Cardiology

Percutaneous transluminal coronary angioplasty (PTCA) has been used successfully to treat atherosclerotic coronary artery disease but has been accompanied by a 30% to 50% rate of restenosis (1). Neointima hyperplasia and vascular remodeling are the main characteristics of the restenosis process. Vascular remodeling involves all three layers of the vessel wall. The migration of smooth muscle cells (SMC) from the adventitia into the site of arterial injury, the proliferation of SMC's to form a neointima, as well as production of extracellular matrix proteins are all considered necessary for the restenosis process (2–4).

A promising new avenue for the reduction of restenosis comes from recent animal studies and pilot clinical trials using intracoronary radiation (IR) (5). However, subacute and late thrombosis are considered to be major problems associated with IR (6). It is of primary interest to reduce the attendant complications of IR, as well as to adjust the radiation dose required to achieve a reduction in restenosis. Such modulation requires an understanding of the mechanisms by which IR mediates its effect.

Percutaneous transluminal coronary angioplasty causes radial stretching of the artery, medial compression, intramural hemorrhage and dissection within the media and the adventitia. Exposure of blood to the injured arterial wall induces thrombus formation and inflammation in the dissection plane. Recent animal studies have demonstrated that dissections are repaired seven days after angioplasty (7). However, in human studies, dissections are usually healed 6 months after angioplasty (8,9). In contrast, two recent studies found in an intravascular ultrasound study that only 56% of dissections resolved at six months follow-up after PTCA and IR without stent implantation (10,11). The phenomenon of unhealed medial dissections appears to be restricted to nonstented arteries, in which the stent itself eliminates the presence of unhealed medial dissections. Findings similar to those of Meerkin et al. (10) have not been reported in studies in which patients with in-stent restenosis were treated with IR (12).

None of the studies discussed above assessed in detail the

From the *Cardiovascular Research Institute, Washington Hospital Center, Washington, DC; and the †Department of Radiation Oncology, Washington Hospital Center, Washington, DC.

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Abbreviations and Acronyms

DA	= dissection area
FL	= fracture length
IA	= intima area
IR	= intracoronary radiation
PTCA	= percutaneous transluminal coronary angioplasty
SMC	= smooth muscle cell
TA	= thrombus area

extent of medial dissection after PTCA and IR. The purpose of this study was, therefore, to quantify the healing response of porcine coronary arteries injured by balloon overstretch with and without subsequent IR at two weeks after intervention, in order to assess the possible role of nonhealed dissections in the thrombosis and restenosis processes.

METHODS

Balloon overstretch injury procedural details. The animals (34 domestic juvenile swine, 30 to 45 kg in weight [Thomas Morris, Inc., Reiserstown, Maryland]) were subjected to overstretch balloon injury in a total of 40 coronary arteries as described previously (13,14). Briefly, the animals were sedated with a combination of ketamine (25 mg/kg) and xylazine (2 mg/kg) by intramuscular injection, then intubated and ventilated with oxygen (2 L/min), nitrous oxide (2 L/min) and isoflurane 1% (1.5 L/min) using a Harvard respirator. All animals were pretreated with aspirin 325 mg/kg and Ticlopidine 250 mg twice a day, 24 h before the procedure and for 14 days after the procedure.

After placement of an introducer sheath in the right carotid artery by surgical cutdown, each animal received a single dose of heparin (150 U/kg). Under fluoroscopic guidance, an 8F hockey stick guiding catheter was positioned in the left coronary ostium. After the intracoronary administration of nitroglycerin (200 μg), coronary angiography was performed and recorded on cinefilm (Phillips Cardiodiagnost, the Netherlands).

Coronary overstretch injury was performed with an angioplasty balloon 30% larger in size than the reference vessel diameter, which was positioned in the proximal segments of three coronary arteries (the left anterior descending, left circumflex or the right coronary artery), inflated to 10 atm three times for 30 s in each artery. After the completion of the injury, the angioplasty balloon was withdrawn, and a final angiography was then performed to assess vessel patency and degree of injury. The vessels were then assigned randomly to receive either radiation or no treatment. After irradiation, the delivery catheter and the guiding catheters were removed and the carotid cutdown repaired. Nitroglycerin ointment (1 in) was administered topically, and the animals were returned to routine care.

Radiation procedural details. After the balloon injury, a closed-end lumen catheter with marker was positioned over the injured site for use to deliver radiation dose. The position of the catheter was checked with fluoroscopy to ensure adequate coverage at both ends of the injured site. The radiation source used for this study was ^{90}Y wire from Schneider (Bulach, Switzerland; n = 18 arteries), a centered beta-emitting source. Dosimetric calculations were carried out using the TG43 algorithm (15) with data generated by Monte Carlo calculations after TG60 recommendations (16). The dose prescription point was 1.2 mm from balloon surface, as described previously (17). The source was left in the catheter for a period sufficient to deliver the prescribed dose of 18 Gy.

Histomorphometry. The animals were euthanized two weeks after treatment. The treated arteries were perfusion fixed. The injured segments were dissected free from the heart, and serial 2 to 3 mm transverse segments were processed and embedded in paraffin. Cross-sections (5 μm) were stained with hematoxylin and eosin and Verhoeff van-Giesson elastin stain. Histology was examined by an experienced observer blinded to the treatment group. Each specimen was evaluated for the presence of neointima formation, luminal encroachment, medial dissection, alteration of the internal and external elastic lamina and morphological appearance of the cells within the media, adventitia and neointima.

Histomorphometric analysis was performed on each segment with evidence of medial fracture. The histopathological features were measured using a computerized PC-compatible image analysis program (Optimas 6; Optimas, Inc., Bothell, Washington). Verhoeff van-Giesson elastin-stained sections were magnified at 7.5×, digitized and stored in a frame-grabber board (DAGE-MTI, Michigan City, Indiana). The arc length of the medial fracture, traced through the neointima from one dissected medial end to the other, was used as a measure of the extent of injury. Area measurements were obtained by tracing the thrombus perimeter (mm^2), neointima perimeter (intimal area, mm^2, defined by the borders of the internal elastic lamina, lumen, media and external elastic lamina), external elastic lamina (vessel area, mm^2) and adventitia (adventitial area, mm^2). To correct for extent of injury, the ratio of intimal area to fracture length (IA/FL) was obtained. Thrombi were identified and designated as luminal or nonluminal (mural), depending on their predominant location in the artery: luminal thrombi were those thrombi in which >75% of the thrombus was present in the lumen, whereas nonluminal thrombi were those thrombi in which >75% of the thrombus was present either between the media and the adventitia or completely in the adventitia. Area measurements were obtained for both luminal and mural thrombi by tracing the perimeter (thrombus area [TA], mm^2). Dissection was defined as a protuberant thick flap between media and adventitia with internal elastic lamina rupture and medial laceration. A medial flap was defined as a thin protuberance into the lumen. A mural dissection was defined as a gap between media and adventitia without association to the

Table 1. Results of Computer-Assisted Histomorphometric Analysis of Thick Sections from Arteries of Pigs in Control and Radiation-Treated Groups in Arteries With Injury

	Control	18 Gy of ^{90}Y	p Value
Adventitia area (mm^2)	2.90 ± 0.76	1.76 ± 0.56	NS
Vessel area (mm^2)	7.11 ± 2.37	8.01 ± 2.33	NS
Lumen area (mm^2)	4.21 ± 2.42	6.43 ± 2.27	< 0.001
FL (mm^2)	2.21 ± 1.06	3.02 ± 1.20	NS
IA (mm^2)	1.15 ± 0.67	0.09 ± 0.10	< 0.001
IA/FL	0.55 ± 0.29	0.05 ± 0.09	< 0.001

FL = fracture length; IA = intima area.

Porcine coronary arteries were injured by balloon overstretch and subsequently treated with either 0 or 18 Gy of ^{90}Y prescribed to 1.2 mm from the balloon center. Histomorphometric analysis was carried out 14 days later.

internal elastic lamina fracture. Dissection area measurements were obtained by tracing the perimeter (dissection area [DA], mm^2). Additionally, the length and the thickness of the dissection were assessed. Furthermore, we calculated the ratio between mural TA:DA.

Immunohistochemistry. Five-μm sections were deparaffinized and incubated with blocking solution (Shandon-Lippshaw, Pittsburgh, Pennsylvania; 1h, room temperature). The sections were incubated with anti-human factor VIII (INC Chemicals, Costa Mesa, California) for 1.5 h at 37°C in a humidified chamber. A universal biotinylated secondary antibody (Shandon-Lippshaw, Pittsburgh, Pennsylvania; 40 min, room temperature) was then applied, followed by alkaline phosphatase conjugated to streptavidin (Vector Laboratories, Burlingame, California; 40 min, room temperature). Staining was visualized using the Red Substrate Kit I (Vector Laboratories). Sections were then counterstained with Meyers' hematoxylin and coverslipped.

Statistical methods. Comparisons between the control and irradiated groups were made using either one-way analysis of variance followed by the Bonferroni post-hoc test for groups whose standard deviation of the means was not statistically different ($p > 0.05$ by Bartlett's test) or by the Kruskall-Wallis analysis of variance followed by Dunn's test for groups whose standard deviation of the means was statistically different ($p < 0.05$ by Bartlett's test). Analysis for correlation was made using Spearman rank-correlation. Differences in rates were analyzed by chi-square analysis. Statistically significant differences between treatment groups were considered to be those with $p < 0.05$.

RESULTS

In this study we utilized 34 animals in which 40 arteries were subjected to balloon overstretch injury and subsequently treated with 0 Gy (n = 22) or 18 Gy (n = 18). All arteries were examined 14 days after treatment. The neointima from ^{90}Y irradiated arteries was markedly smaller in size than the controls, as demonstrated earlier (18). The majority of the sections exhibited a virtual absence of neointima formation. The quantitative histomorphometry results of the balloon injured and irradiated versus control arteries are shown in Table 1. These results demonstrate a statistically significant reduction of IA/FL after treatment with 18 Gy ^{90}Y ($p < 0.01$).

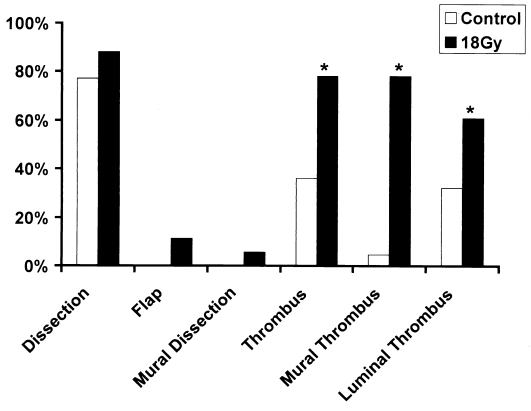

Figure 1. Distribution of thrombus and dissection from pig arteries after balloon injury with and without radiation. Porcine coronary arteries were injured by balloon overstretch and subsequently treated with either 0 or 18 Gy of ^{90}Y prescribed to 1.2 mm from the balloon center. Treated arteries were analyzed 14 days after treatment (*$p < 0.05$ Control vs. 18 Gy).

When present, the cells of the neointima in the 18 Gy group were morphologically similar to controls. There was no evidence of necrosis in the irradiated arteries or excess of fibrosis compared with the control balloon injured arteries. Histologically, control-treated balloon-injured arteries exhibited substantial neointima consisting mostly of stellate and spindle-shaped cells in a loose extracellular matrix, which was largely absent in arteries treated with ^{90}Y.

The extent of thrombosis has been reported to affect the extent of restenosis (1,19). At 14 days, we did not apply a minimal thrombus area as an inclusion criterion for this analysis. Significant differences were observed between control and irradiated arteries with regard to the presence of thrombi, 8/22 (36%) versus 14/18 (78%) (control vs. IR: $p < 0.001$) (Fig. 1).

We next scored the injured arteries for the presence of luminal or mural thrombi. The presence of both mural and luminal thrombus was increased significantly in the irradiated group. Mural thrombi were present in 1/22 (4.5%) of the control injured arteries as compared with 14/18 (78%) in the irradiated group. Luminal thrombi were present in 7/22 (32%) of the control injured arteries as compared with 11/18 (61%) of the irradiated arteries ($p < 0.01$ for both luminal and mural thrombus rates; Fig. 1). However, total thrombus area was larger in the control group compared with the 18 Gy group, as reported previously (6). Thrombi in control arteries were not significantly larger, whereas mural thrombus area was significantly increased in irradiated arteries (Table 2).

Dissections of the media have been associated with mural thrombosis and restenosis (20–23). Therefore, we analyzed the incidence of dissection in an attempt to further elucidate the effects of IR on arterial healing. We first analyzed the presence of any dissection, whether healed (reattached to the external elastic lamina) or not. As shown in Table 2, a similar overall rate of dissection was observed in the two

Table 2. Parameters of Dissection and Thrombus After PTCA With and Without Irradiation

	Control	18 Gy of ^{90}Y	p Value
TA, mm^2	0.44 ± 0.80	0.39 ± 0.33	< 0.05
MT area, mm^2	0.01 ± 0.01	0.29 ± 0.30	< 0.001
LT area, mm^2	0.40 ± 0.77	0.10 ± 0.18	NS
DA, mm^2	0.19 ± 0.28	0.32 ± 0.29	< 0.05
Dissection length, mm	1.10 ± 0.88	1.17 ± 0.64	NS
Dissection thickness, mm	0.25 ± 0.18	0.33 ± 0.32	< 0.05
MT/DA	0.01 ± 0.05	0.74 ± 0.43	< 0.001

DA = dissection area; LT = luminal thrombus; MT = mural thrombus; TA = thrombus area.

Porcine coronary arteries were injured by balloon overstretch and subsequently treated with either 0 or 18 Gy of ^{90}Y prescribed to 1.2 mm from the balloon center. Treated arteries were analyzed 14 days after treatment.

groups, 17/22 (77%) for the control group and 16/18 (88%) for the irradiated group (chi-square = NS). Furthermore, no difference was observed between the two groups for the dissection length, thereby confirming a similar degree of injury in the two groups. In contrast, free medial flaps (not attached to the external elastic lamina) were observed only in the irradiated group in two cases, and a mural dissection was further observed in one irradiated artery. As demonstrated in Table 2, we also observed a significant increase of the dissection area in the irradiated group (0.19 ± 0.28 vs. 0.32 ± 0.29 mm^2; $p < 0.05$).

We also observed qualitative differences between control and irradiated arteries with regard to dissections. The dissection plane and clefts extended frequently into the lumen in both groups. However, the vascular response on the dissection site appeared to be different. In the control group, the dissection area consisted essentially of neointima (Fig. 2). In the IR group, however, the area between the dissected media and the external elastic lamina was filled partially by thrombus, or a small neointima was generally observed (Fig. 2). A positive relation between IA and dissection area was observed only for the control group (Fig. 3, $R^2 = 0.474$; $p < 0.003$; $alpha_{0.05} = 0.862$).

Vessel size or extent of injury may also affect the degree of thrombosis (21). We demonstrated a significant increase in the ratio mural TA:DA upon treatment with IR (0.01 ± 0.05 vs. 0.74 ± 0.43; $p < 0.001$). Correlation studies demonstrated a positive relation between mural TA and DA only for the irradiated group (Fig. 3; $R^2 = 0.889$; $p < 0.001$; $alpha_{0.05} = 1.00$).

Endothelial coverage of the repaired intima as determined by the presence of a continuous layer of factor VIII-positive cells was observed in all control arteries. In contrast, the irradiated arteries only showed a complete endothelial layer in the uninjured part of the cross-section, whereas between the two media tears the endothelial coverage was not completed at the investigated time point.

DISCUSSION

Our study suggests that IR is not associated with any difference in the rate of dissection between control and irradiated arteries. The control group exhibited a smaller dissection area and fewer mural thrombi as compared with the IR group, which is in accordance with the hypothesis of the evolution of the healing by neointima (20,24). A strong positive correlation was observed between dissection area and neointima area in the control group only, which suggests that IR can overcome the proliferative stimuli induced by this injury. In contrast, a positive correlation between mural thrombus area and dissection area was observed in the irradiated group only, which suggests that IR delays the healing and reendothelialization of these dissections.

Morphological studies indicate that the principle of severity of injury applies to both animal and human studies (25,26). However, the variability in the response of an atherosclerotic artery to PTCA injury results from a combination of dissection, thrombus formation and cellular responses to injury as well as variable scar contraction and elastic recoil (7,26–28).

Little is known about the effect of IR on repair of vascular

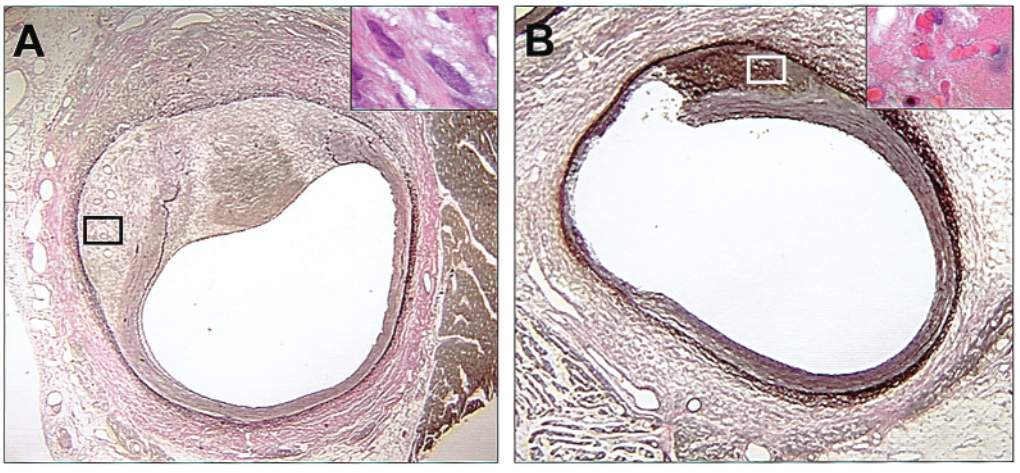

Figure 2. Cross-section of **(A)** control artery and **(B)** irradiated artery 14 days after intervention. Similar dissection area in both arteries. **(A)** shows the dissection area filled with neointima and severe luminal stenosis. **(B)** shows mural thrombus with red and white blood cell, platelet and fibrin deposition and a wide open lumen; van-Giesson staining, magnification 7.5×.

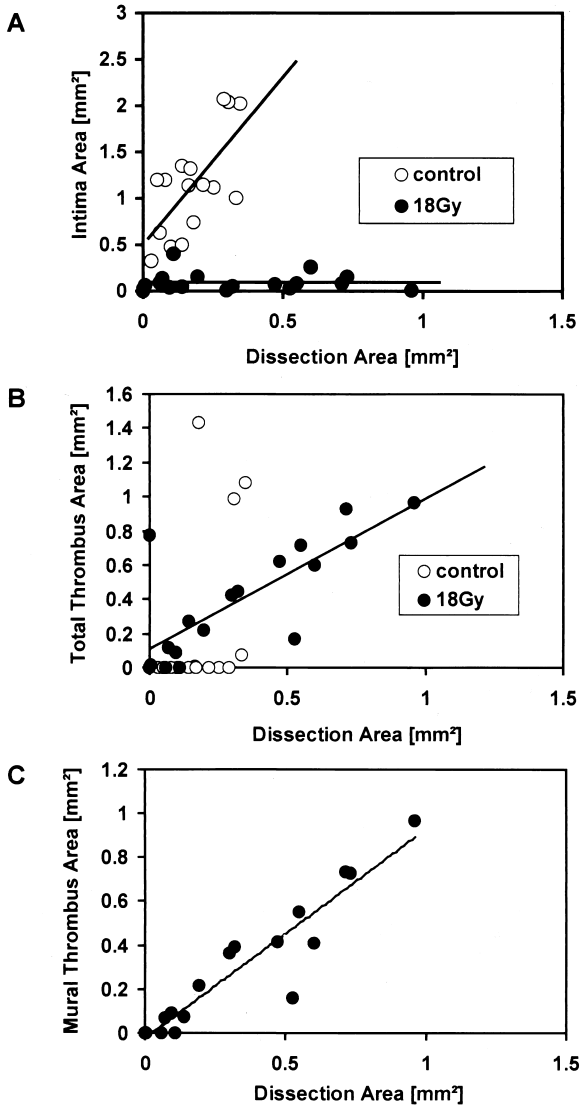

Figure 3. **(A)** Correlation between dissection area and intimal area in the two groups. **(B)** Correlation between dissection area and total thrombus area in the two groups. **(C)** Correlation between dissection area and mural thrombus area in the irradiated groups. Porcine coronary arteries were injured by balloon overstretch and subsequently treated with either 0 or 18 Gy of ^{90}Y prescribed to 1.2 mm from the balloon center. Treated arteries were analyzed 14 days after treatment.

injury and its relationship to thrombosis. Increasingly, however, investigators are faced with the problem of delayed healing and associated thrombosis (20,29–31). Further, the potential causes of late thrombosis after IR in humans have been discussed earlier; they are delayed reendothelialization, fibrin deposition and platelet recruitment, impaired vasoractivity, tissue erosion around the stent and unhealed dissections (32).

In our study, we observed an incomplete reendothelialization in all irradiated arteries between the medial tears. Earlier, Detre et al. (27) reported that irradiation inhibits endothelial cells migration leading to a reduction in migratory function of irradiated endothelial cells that may be responsible for potential endothelium-related dysfunction.

We have described and quantified previously that porcine coronary arteries treated with IR exhibited an overall increased rate of predominantly mural thrombosis (6). Herein, we have quantified for the first time in an animal model what may be the cause of this thrombosis, namely the unhealed medial dissections. Tears or dissections involving the intima, media or adventitia have been observed at necropsy in post-angioplasty patients (33–36). The internal elastic lamina was disrupted in both groups in direct proportion to the degree of neointimal proliferation only in the control group, as described previously by Gravanis and Roubin (37). Our results were in agreement with previous animal studies, which described complete repair of medial dissections by seven days after PTCA (7,38). In the control group of this study, accumulation of neointimal tissue appears to act like a "biological stent," stabilizing the coronary dissection and maintaining the integrity of the vessel; we hypothesize that this process results in reduced mural thrombosis. Of course, this biological repair is associated with severe luminal stenosis through a combination of intimal hyperplasia and unfavorable remodeling (24,39). The vascular response to changes in flow and shear stress is a very important determinant of remodeling and is likely determined by the structure of the vessel wall (24). Intracoronary radiation further showed a global favorable remodeling in the porcine model (17). Changes in shear and flow caused by the presence of nonhealed medial dissections could also enhance the formation and propagation of thrombi.

The beneficial value of stenting medial dissections is well known (40,41). Intracoronary radiation is rapidly emerging as a front-line therapy for in-stent restenosis since no alternative therapy can reduce intimal hyperplasia dramatically. In addition, late stent thrombosis has clearly emerged as one of the major problems after IR (11,32). However, these investigators also reported that small dissections, which were not obviously seen angiographically, may contribute to late thrombosis (42). Adjunct therapies may be designed to reduce these complications of IR and, thereby, result in the ideal blend of a potent antimitotic treatment and a therapy to enhance healing or reduce thrombosis.

Study limitations. The main limitation of this study was the use of tissues obtained at only one time point and one dose of radiation derived from only one isotope. The porcine restenosis model also has several limitations: it is primarily a neointima formation model, and, although the normal pig coronary resembles the normal human coronary, there is no atherosclerosis as in the human PTCA setting. Furthermore, there is considerable variability in the amount of injury that influences the proliferative response. Nonetheless, in this study we demonstrated a marked inhibition of neointima formation and repair of the arterial injury with radiation treatment. This is an important aspect of the arterial response, as the extent of injury determines the thickness of the neointimal hyperplasia. In the absence of a stent, the degree of neointima formed is highly variable even

in the control group, presumably not only because of individual differences in the degree of injury but also because of the individual responses of each animal (43). This study does not provide stenting data, and we anticipate that stenting will resolve dissections as demonstrated in clinical trials (9). The analysis of luminal reendothelialization using factor VIII immunostaining can only estimate the endothelial coverage. A more sensitive approach, such as scanning electron microscopy, may improve the understanding of vascular reendothelialization after IR. Functional studies, such as stimulative tests for vascular dilatation, may also help the understanding of the quality of the endothelium after IR.

Conclusions. We suggest that the dissection area may be a useful parameter to quantify the extent of injury after overstretch balloon injury with or without subsequent IR. Furthermore, we conclude that coronary injury is not associated with an increased rate of dissection after IR but instead is associated with more nonhealed dissections and large mural thrombi. Whether these findings observed in nonatherosclerotic porcine coronary arteries can be extrapolated to diseased human coronary arteries is unclear. However, these findings may influence the design of human trials of intravascular irradiation at the time of angioplasty. Better understanding of the nature of the vascular responses after injury may aid in developing therapeutic strategies for increased benefit of IR.

Reprint requests and correspondence: Dr. Ron Waksman, Vascular Brachytherapy Institute, Cardiovascular Research Institute, Suite 4B-1, Washington, DC 20010. E-mail: rxw8@mhg.edu.

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